IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/485,512
Applicant	:	Johnson et al.
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TC/A.U.	:	1648
Examiner	:	Ulrike Winkler
For	:	RECOMBINANT PORCINE ADENOVIRUS VECTOR
Docket No.	:	2-00
Customer No.:		23713

Confirmation No. 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND DECLARATION OF DR. JEFFREY MICHAEL HAMMOND
37 C.F.R. § 1.132

1. Background of Declarant.

I am a co-inventor of the above-captioned application. I have over 25 years of experience in the field of animal health, including research, development, and applications in the areas of virology, diagnosis, epidemiology, immunology, and molecular biology. I have expertise in the development of adenoviral vectors and vaccines, particularly in the development of porcine adenovirus recombinants. I obtained an Honours Degree in Immunology from the North East Surrey College of Technology in London. Through London University, I completed a PhD in Virology and Molecular Biology focusing on African swine fever virus and construction of vaccinia virus recombinants. I am currently a Senior Research Scientist within the Vaccines and Therapeutics Program at the Commonwealth Scientific & Industrial Research Organisation's Australian Animal Health Laboratory in Geelong, Victoria.

2. Incorporation by reference of Declaration submitted on April 1, 2003.

I hereby reaffirm and reassert my Declaration signed on March 31, 2003 and submitted on April 1, 2003 (hereinafter the "First Declaration") and incorporate the same herein by reference thereto.

3. Purpose of the declaration.

This Declaration presents, for the Examiner's consideration in the above-captioned invention and application, material including various facts and information in support of the patentability of pending claims 1, 2, 4, 25-32, 39-42, 44, and 51 (currently rejected under 35 USC 112, 1st paragraph) and claims 45-50 and 52-62 (currently withdrawn). This material is submitted in a spirit of forthrightness.

4. Claim amendments.

The claims have been amended to specify insertion sites comprising a right hand end of said genome wherein said right hand end comprises from about 50 genomic map units to about 100 genomic map units. This language is supported by ordinary usage in the art. One of ordinary skill in the art would understand that a genome map for any porcine adenovirus can be conventionally portrayed in arbitrary map units from 0 to 100 units and that the terminology of left hand end and right hand end properly designates the left and right sides or halves, meaning that the left end corresponds to a region of from 0 to 50 map units and that the right end corresponds to a region of from 50 to 100 map units. Thus the right hand end (rhe) is defined herein as 50 to 100 genomic map units.

5. The invention satisfies the written description and enablement requirements. The disclosure and knowledge in the art at the time of filing were sufficient to show that at the time the invention was made, the Applicants had possession of and enabled the invention as claimed.

a. The invention as claimed according to the presently amended claims is fully supported by the specification and complies with the written description and enablement requirements. Information in the specification and knowledge in the art available at the time of the priority date provides adequate structural information of the PAV genome to allow the person of ordinary skill in the art to insert heterologous sequences into the right hand end, extending from about 50

map units to about 100 map units of the genome, of genomes in the genus of porcine adenoviruses.

b. The full sequence of the PAV 3 genome was published by Reddy et al in 1998 (Reddy PS, Idamakanti N, Song J.Y., Lee J.B., Hyun B.H., Park J.H., Cha S.H., Bae Y.T., Tikoo S.K. & Babiuk L.A. (1998). Nucleotide sequence and Transcription Map of Porcine Adenovirus Type 3. Virology 251, 414-426), subsequent to the filing of the present application. At the priority date, there was some partial sequence information available in the public domain, which together with the teaching of the specification would have allowed the skilled person to insert a heterologous sequence in the rhe as defined herein without undue experimentation.

c. As stated by Dr. Hammond in his First Declaration, (see e.g., page 4, third full paragraph) in the process of cloning the three leader sequences, the late genes of the PAV3 genome (hexon and penton) were located and sequenced. The nucleotide sequence encoding the penton protein of PAV3 was published in 1996 (McCoy R.J., Johnson M.A., Studdert M.J., Sheppard M. Genomic location and nucleotide sequence of a porcine adenovirus penton base gene. Arch Virol. 1996; 141 (7): 1367-75). The nucleotide sequence encoding the hexon protein corresponds to approximately 55 to 65 map units. This sequence information was submitted to Genbank in August 1995 (Genbank Accession No. U34592) and published in 1996 (McCoy R.J., Johnson M.A., Sheppard M. Nucleotide and amino acid sequence analysis of the porcine adenovirus 23K protein. DNA Seq. 1996;6(4):251-4.) and was therefore available as public knowledge before the priority date. Thus the skilled person could have used this information for flanking sequences for construction of expression cassettes for insertion in the rhe as defined herein and in particular, for insertion in regions other than the regions disclosed in the specific examples of the present application.

d. Sequence information of the late region (L5) of the PAV3 genome (approximating to map units 72 to 85) was submitted to Genbank in December 1996 (Genbank Accession No. U82628) and published in 1997 (McCoy R.J., Sheppard M. and Johnson M.A., Nucleotide and amino acid sequence analysis of the 100K protein of a serotype 3 porcine adenovirus. DNA Seq. 1997; 8(1-2)59-61. Thus the skilled person could have used this information for flanking sequences for construction of expression cassettes for insertion in the rhe as

defined herein and in particular, for insertion in regions other than the regions disclosed in the examples of the present application.

e. Sequence information of the late region (L3) of the PAV3 genome (approximating to map units 50 to 55) was published in 1996 (McCoy R.J., Johnson M.A., Sheppard M. Nucleotide and amino acid sequence analysis of the porcine adenovirus 23K protein. DNA Seq. 1996;6(4):251-4.). Thus again the skilled person could have used this information for flanking sequences for construction of expression cassettes for insertion in the rhe as defined herein and in particular, for insertion in regions other than the regions disclosed in the examples of the present application. Once we had provided the promoter and leader sequences and showed insertion at specific sites, it became a matter of ordinary skill in the art to practice insertions into other sites without undue experimentation.

f. The Examiner is correct in stating that there was no information in the art regarding sequences of complete PAV genomes. There was, however, knowledge of partial sequence information available at the relevant time as discussed herein. Such knowledge in combination with the teaching of the specification would have allowed the skilled person to insert a heterologous sequence into the rhe (50 to 100 map units). Knowledge of the structure of a complete PAV genome would not have been required to successfully insert foreign genes into regions other than the PAV regions disclosed as asserted in the Office Action on page 8.

g. I believe that some of the statements in my First Declaration have been misconstrued. The Office Action states at page 4 that the First Declaration "indicates that it is necessary to have an understanding of the structure of the porcine adenovirus in order to determine the major late promoter and the requisite leader sequences." This statement appears to imply that my First Declaration indicated that the complete sequence of porcine adenovirus needed to have been known in order to determine the major late promoter and leader segments. The Office Action then states that this sequence information "was not available in the art at the time of filing." As discussed above, the availability of the complete sequence of porcine adenoviruses was not crucial.

In the First Declaration, the purpose of my statement was to discuss and contrast the differences between HAV and PAV and conclude that the teaching relating to HAV was not applicable to PAV.

I further discussed the technical difficulties encountered in making the invention including the construction of the major late promoter leader sequences expression cassette and state that the knowledge of HAV sequences was of no value as applied to PAV sequences. I indicated that the construction of restriction maps enabled approximation of the location of the promoter. I did not imply that knowledge of an entire PAV genome structure/sequence was necessary to allow insertions at various points.

In contrast to the idea that there was no structural information available at the time of filing, the reality is that there was partial sequence information available for PAV, but no sequence information available for the promoter elements. Thus, the inventors isolated and sequenced the promoter and leader sequences with the available knowledge of the structure of the PAV and with no reasonable expectation that the teaching of HAV would be applicable to PAV.

h. The isolation and sequencing of the major late promoter leader sequence and the tripartite leader sequences and its disclosure was a significant contribution to the art. The identification of these key control elements allowed the Applicants to construct a major late promoter leader sequence expression cassette to insert a heterologous sequence in the right hand end as defined herein. Our disclosure of not just the promoter and leader sequences in the instant application but also other information such as complete restriction enzyme mapping with multiple enzymes therefore provided a significant understanding and allowed for others of ordinary skill to use that disclosed information along with the partial sequence / structural knowledge publicly available.

6. An Exhibit further illustrates and clarifies the genomic regions demonstrated and claimed as sites of possible insertions.

To aid in clarifying the regions of the porcine adenoviral genome under consideration, the attached Exhibit A has examples of illustrations. Figure A1 illustrates the entire genome map of PAV3 on a scale of arbitrary map units.

Figure A1 illustrates the E3 and *rhe* regions used for gene insertions; these insertions fall within the right hand end of the map as depicted from 50 to

100 map units. The E4 region along with the E3 and rhe regions are thus properly encompassed in the right hand end.

7. The genus claim to all porcine adenoviruses is appropriate given the scope of disclosure and knowledge in the art.

a. The claimed genus reads on all porcine adenoviruses. For example, all serotypes of PAV are included.

b. All PAVs are classified in the genus *Mastadenoviridae*, and there was a strong expectation by the person of ordinary skill in the art at or before the priority date that the genome structure would be conserved across the genus.

b. Regarding genus conservation, attention is drawn to the internet site (not active links) http://www.ncbi.nlm.nlh.gov/ICTVdb/, more precisely at http://www.ncbi.nlm.nlh.gov/ICTVdb/Ictv/index.htm. This is the official site of the international classification system for viruses. The information available on this reference establishes that there is strict conservation of genome organisation among the various serotypes of the PAV. Thus this information verifies that the expectations of the skilled person were correct at the time of the priority date and that the description of PAV3 disclosed in the specification could be applied to all serotypes of the genus. No undue experimentation would be necessary to achieve success using various members of the genus.

8. Declaration is of own knowledge and true.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Jeffrey Michael Hammond — Date 26/2/04

EXHIBIT A

of

Second Declaration of Dr. Jeffrey Michael Hammond

The following examples illustrate genomic regions of PAV.

FIGURE A1
of Second Declaration
(IN COLOR)

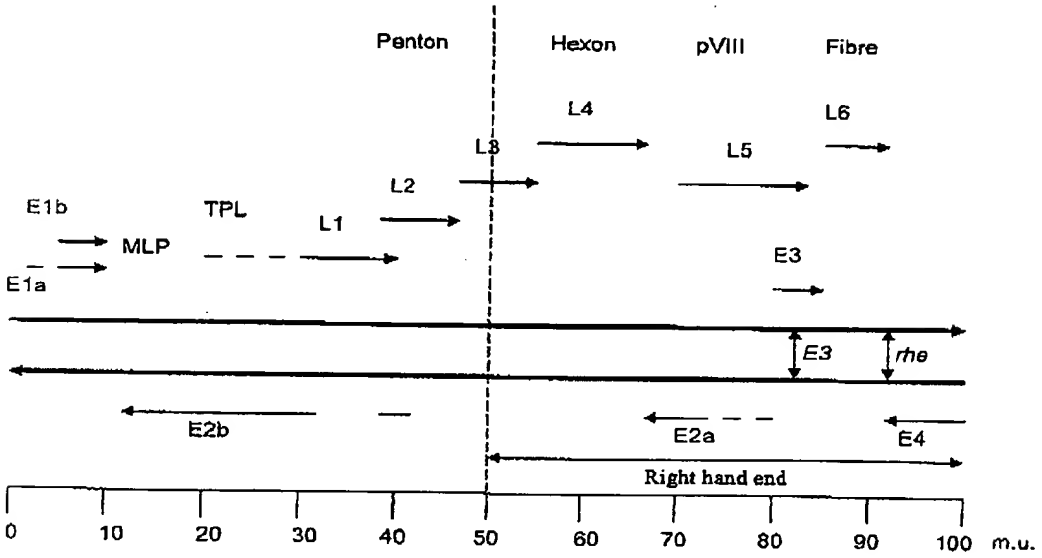

Fig. A1. Entire genome map of PAdV3. The right hand end from 50 map units (m.u.) to 100 map units is indicated as to the right of the red (dotted) vertical line located at 50 map units. The *E3* and *rhe* regions used for gene insertions are shown by red (double-headed) vertical arrows within the region of 50 to 100 map units. The positions of the Major Late Promoter (MLP) and tripartite leader (TPL) sequences are shown.